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DOI: https://doi.org/10.1097/MAT.0000000000000495

ASAIO Journal Publish Ahead of Print

DOI: 10.1097/MAT.0000000000000495

Venoarterial extracorporeal life support for neonatal respiratory failure: indications and impact on mortality

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Running Head Line: Neonatal Venoarterial ECLS Indications

Conflicts of Interest and Source of Funding: We have no conflicts of interest to declare. Dr. Bamat is funded through National Institute of Health (NIH) grant 2T32HD060550-06. The NIH did have not have any direct role or influence in the design, execution or reporting of this study.

Abstract

Venoarterial (VA) extracorporeal life support (ECLS) for neonatal respiratory failure is associated with increased mortality compared to venovenous (VV) ECLS. It is unclear if this is a causal relationship or reflects differences in baseline disease severity between infants managed with these two strategies. Our objective was to identify clinical variables associated with the preferential selection of VA over VV ECLS, as these may confound the association between VA ECLS and increased mortality. We identified documented indications for preferential VA selection through chart review. We then assessed how the presence of common indications impacted mortality. 39 cases met eligibility. Severity of hypotension/degree of inotropic support and ventricular dysfunction on echocardiogram prior to cannulation were the most common specific indications for preferential VA ECLS. Mortality was 12.5% when neither high inotropic support nor ventricular dysfunction was present. Mortality rose to 20% with high inotropic support and 25% with ventricular dysfunction present alone and to 50% when both were present. We conclude that severe hypotension and ventricular dysfunction prior to ECLS cannulation are common indications for VA ECLS that likely influence survival. Research assessing the impact of ECLS cannulation mode on survival should adjust for baseline differences between groups for these important variables.

Keywords: extracorporeal membrane oxygenation; infant, neonate; respiratory insufficiency; intensive care units, neonatal; persistent fetal circulation syndrome.

Providers caring for infants with refractory respiratory failure employ venoarterial (VA) or double-lumen venovenous (VV) cannulation to provide life-saving extracorporeal life support (ECLS). Each mode has distinct advantages and disadvantages that may influence patient outcomes.[1, 2] A notable advantage of VV is single vessel support without need to ligate the right common carotid artery - a disadvantage of VA. However, only VA provides both gas exchange and circulatory support. VV does not provide the latter, relying on native cardiac output for circulation. While sparing the carotid artery is desirable, VA is often preferentially employed when the infant's clinical presentation questions the adequacy of native cardiac output, suggesting greater disease severity. These important baseline differences bias comparisons between ECLS modes on important patient outcomes. Data from the Extracorporeal Life Support Organization (ELSO) registry show 13% greater in-hospital mortality for infants receiving support with VA rather than VV ECLS.[3] While this may reflect harm caused by VA, it may instead simply reflect a strong association between baseline disease severity and both the likelihood of VA selection and death.

The primary aim of this study was to characterize the clinical variables that result in selection of VA ECLS by identifying documented indications for its preferential use in a cohort of neonates with respiratory failure. The second aim was to evaluate how the presence of these clinical variables influences the outcome of in-hospital mortality. Our objective was to identify clinical variables that require consideration when comparing outcome differences between ECLS modes in neonates with respiratory failure.

Methods

We performed a single-center observational study. A descriptive study design was followed by a retrospective cohort design for our primary and secondary aims, respectively. Our institutional review board approved the study.

Population

All neonates without congenital anomalies, born at greater than 35 weeks gestational age and undergoing VA ECLS for respiratory failure within 14 days of life at the Children's Hospital of Philadelphia between January of 2001 and August of 2014 were included. VV or VA modes were considered on a case-by-case basis. Study exclusions were congenital anomalies, discovered before or after birth. This included congenital heart disease, congenital diaphragmatic hernia (CDH) or genetic diseases without gross anatomic anomalies, such as alveolar capillary dysplasia. Although CDH accounts for many ECLS neonatal respiratory failure cases, we chose to exclude this population for two reasons. First, CDH infants differ from other neonates in their underlying pathophysiology. Second, our institution routinely provides VA rather than VV ECLS for CDH. As such, evaluation of this diagnostic subgroup was not applicable to the objective of characterizing the indications resulting in the preferential use of VA over VV ECLS.

Data Collection

Initial screening for eligibility was performed through a database containing all ECLS cases performed in our neonatal unit. This database includes primary diagnosis, age at cannulation and mode of ECLS support. Following exclusions, two authors performed a detailed chart review to confirm eligibility and identify the indication for preferential use of VA ECLS.

A primary indication for VA ECLS was assigned only when medical documentation clearly described the reasoning for selection of this mode. Instances in which a primary indication was not clearly documented were categorized as "unclear or not specified." An exception was made when cannulation occurred emergently during ongoing chest compressions for cardiopulmonary resuscitation – based on our clinical practice we felt this to be a self-evident indication without need for explicit documentation justifying the selection of VA.

For the second aim, we assessed how the presence of common VA indications impacted in-hospital mortality. All cases were assessed for the presence of pre-cannulation variables most commonly found to be VA indications. Presence of the variable was determined by pre-specified definitions (see section "1.3 Definitions") irrespective of whether or not provider documentation suggested this was the indication for VA selection. For example, a patient may have been described as having undergone VA ECLS due to the degree of inotropic support yet not meet pre-defined criteria for "High Inotropic Support" for this second objective. Additional variables collected from the ELSO registry and/or through medical chart review included birth weight in kilograms, gestational age in weeks, sex, race, one minute Apgar score, primary diagnosis, oxygenation index and in-hospital mortality. Occasional missing data for one minute Apgar score and oxygenation index are reflected within the variable row heading in Tables II and III.

Definitions

For the characterization of primary indications, "Severity of Hypotension/Inotropic Support" includes cases in which medical documentation

indicated that the severity of hypotension and/or degree of inotropic support was the primary reason for the selection of VA over VV ECLS. “Ventricular Dysfunction on Echocardiogram” includes all cases in which documentation indicated that findings from an echocardiogram reporting ventricular dysfunction were the primary indication for VA. A variety of additional specific clinical circumstances were documented as primary indications without appearing more than twice. The qualifying term “Clinical/Not Otherwise Specified (NOS)” indicates clinical impressions that were clearly specified as the indication for VA ECLS but without elaboration as to the objective findings that resulted in that clinical impression. “VV Not Attempted Due To Patient Size” specifies cases in which VA was used without an attempt to place a VV cannula due to patient size, while “VV Attempted, Unable to Insert” denotes cases in which VA was used following a failed attempt to place a double-lumen VV cannula.

For the second aim of evaluating the impact of common indications for VA on mortality, “High Inotropic Support” was defined as dopamine monotherapy in excess of 15 micrograms per kilogram per minute or use of multiple inotropic agents. This was a pragmatic definition reflective of our institution’s typical practice of using dopamine monotherapy as a first line agent, followed by dose escalation and/or use of additional medications for refractory hypotension. “Ventricular Dysfunction on Echo” was noted as present when echocardiography performed prior to cannulation documented moderate, moderate to severe or severely diminished ventricular systolic shortening or reported “poor” function or frank “dysfunction” for either right or left ventricle. In contrast, documentation of mild or mild to moderately diminished ventricular systolic shortening or reported “low normal”, “mild dysfunction” or “normal” function for both ventricles

did not meet criteria. On the basis of the presence of these two common indications, the variable "VA Indications Status" was generated to classify subjects as "Neither", "High Inotropic Support Only", "Ventricular Dysfunction Only" or "Both" for subsequent analysis.

Statistical Analysis

Data was summarized using frequency counts and percentages, means and standard deviations for parametric data and medians and interquartile ranges for non-parametric data. We compared "VA Indications Status" groups as follows: unadjusted univariate comparisons of continuous dependent variables were performed with analysis of variance for parametric data and Kruskal-Wallis for non-parametric data, categorical outcomes were performed with Fisher's exact test. Multivariate logistic regression was used to assess the adjusted impact of "VA Indications Status" on in-hospital mortality. Model selection assessed all collected variables as candidate explanatory covariates. Variables resulting in a likelihood ratio test with $p < 0.20$ when added to a model restricted to "VA Indications Status" were included in the final multivariate model. An alpha level of $p < 0.05$ was considered statistically significant. Analyses were performed using STATA/IC 13.0 software (Stata Corp., College Station, Texas.)

Results

273 infants underwent ECLS in our neonatal intensive care unit within the study period. Using our clinical database to screen, we excluded 135 infants with congenital anomalies (including CDH) and 15 infants older than 14 days at ECLS cannulation. Of the remaining 123, we excluded the 80 (65%) for which VV ECLS was selected. Chart review of the remaining 43 cases resulted in 4 additional exclusions for congenital

anomalies, resulting in a study cohort of 39 infants for whom VA ECLS was selected. This process is summarized in Figure 1.

The results of our first aim are displayed in Table I. A primary indication for the selection of VA ECLS was clearly documented in 26 of 39 (69%) cases. Specific clinical concerns resulted in VA selection in 23 (59%). Of these, concerns regarding the severity of hypotension and/or degree of required inotropic support (6 cases, 15%) and evidence of ventricular dysfunction on an echocardiogram prior to cannulation (4 cases, 10%) were the most common specific clinical indications for VA selection. Several other specific clinical indications documented twice or less are listed in Table I. Four cases (10%) required VA ECLS as part of ongoing cardiopulmonary resuscitation with chest compressions. Technical size limitations associated with the use of a double lumen VV cannula resulted in use of VA ECLS in 4 (10%) cases. Of these, 3 were unsuccessful attempts to place a VV cannula; in the remaining case no attempt was made on the basis of patient size. The remaining 12 (31%) cases lacked clear medical documentation describing the rationale for VA selection. Baseline characteristics of infants undergoing VA ECLS for clinical, technical or unspecified indications are provided in Table II. There were no statistically significant differences between groups. All four infants for whom VA ECLS was chosen because of technical limitations survived. In contrast, 25% (3/12) of infants for whom a primary indication was unspecified and 35% (8/23) of infants for whom a clinical concern resulted in VA ECLS, died.

For our second aim, we compared infants of the basis of the absence or presence of high inotropic support and ventricular dysfunction on echocardiogram. Baseline characteristics between groups are displayed in Table III. There were no statistically

significant differences. The impact of VA ECLS on mortality is depicted in Figure 2. Mortality was 12.5% when neither high inotropic support nor ventricular dysfunction was present. Mortality rose to 20% with high inotropic support in isolation and to 25% with ventricular dysfunction in isolation. The presence of both concurrently was associated with 50% mortality. A mortality outcome was ascertained for all subjects, with no missing data. Gestational age, birth weight and Apgar score at one minute met criteria for covariate inclusion in the multivariate analysis. Increasing birth weight and gestational age were associated with a trend towards increased mortality risk, while increasing Apgar score was associated with a trend towards decreased mortality. The impact of these variables and VA ECLS indications on in-hospital mortality in both univariate and multivariate adjusted analysis is summarized in Table IV.

Discussion

To our knowledge, this is the first study systematically characterizing the clinical variables resulting in the selection of VA ECLS and assessing the impact of their presence on neonatal mortality. We found that clinical concerns surrounding the degree of cardiorespiratory compromise were the most common indications, with the severity of inotropic refractory hypotension and evidence of ventricular dysfunction on echocardiogram being the two most common specific indications.

No infant placed on VA ECLS for technical indications died, compared to 35% of infants placed on VA ECLS due to clinical concerns. As depicted in Figure 2, the presence of either high inotropic support or echocardiographic evidence of ventricular dysfunction in isolation was associated with an approximate doubling in the risk of

mortality. When both were present, the mortality risk was four-fold. Adjustment for confounding variables only further amplified the effect size of these associations.

Our results are important for two reasons. First, they have implications for survival prognostication. Clinicians and parents should appreciate that factors present at the time of cannulation may considerably influence mortality. Second, our results have important implications for further clinical research on this topic.

It remains unclear if the use of VA over VV ECLS causes increased mortality. Reports of a survival benefit for VV when not accounting for group differences are challenged by reports suggesting its absence when accounting for baseline group differences or restricting the study cohort to similar patients.[4-7] Recently, a large retrospective report of the ELSO registry by Smith and colleagues shows persistence of an independent mortality risk associated with VA mode after adjustment for baseline differences between groups through multivariate logistic regression.[8] This contemporary, well-designed analysis may represent the best approximation of any true difference. However, the study authors acknowledge that a persistent confounding bias likely exists. Authors of recently published reviews agree that available data is limited by the presence of confounding bias, and further, that currently available ELSO registry data are unable to provide insight into whether differences between VA and VV ECLS are "due to patient selection, severity of illness, or an inherent benefit of the particular mode."[2,3] These limitations are due to "residual confounding" – persistent bias from unaccounted differences between groups that are either not collected or collected with insufficient precision to discriminate important differences. Our results highlight two likely principal sources of residual confounding. With respect to degree of inotropic refractory

hypotension, registry data identifies inotropic agents used prior to ECLS, but does not provide more precise information, such as medication dose. The vast majority of neonates requiring ECLS receive some degree of inotropic support.[9] Thus, useful discrimination between high and low risk groups on the basis of this variable requires characterization beyond the mere absence or presence of an inotropic agent. The registry does not collect data on pre-cannulation echocardiographic findings. We found that the extent of inotropic refractory hypotension and ventricular dysfunction prior to cannulation are the most common drivers of VA selection and influence survival. Thus, accounting for baseline differences in these characteristics is critical to any unbiased approximation of mortality differences.

Despite a possible association with increased mortality, increased central nervous system injury and concerns regarding the long-term health consequences of carotid artery ligation, VA remains the most commonly used ECLS mode in our study population. Between 2001 and 2010, in excess of 50% of cases reported to the ELSO registry were performed with VA.[8] It is therefore likely that VA is often used for cases amenable to VV ECLS. Better characterizing unbiased outcome differences would inform decision making for clinicians uncertain about the benefit or harm of using VA ECLS judiciously.

We speculate that even in the absence of technical limitations, there exists a population of infants for whom VA ECLS, and the direct circulatory support it provides, is beneficial. The challenge remains to identify which patient will benefit. Published guidelines have suggested that hemodynamic instability including hypotension, high doses of inotropic drugs and severe myocardial dysfunction are contraindications for VV ECLS.[10] However, successful VV ECLS use despite significant hypotension and

inotropic support has been reported in several studies, most notably a report by Roberts and colleagues in which pre-cannulation inotropic support scores were assigned to all infants.[9, 11,12] We are not aware of published reports of VV ECLS in a cohort of neonates with echocardiographic evidence of ventricular dysfunction prior to cannulation. However, Strieper and colleagues report improvement in ventricular dysfunction following initiation of VV ECLS in neonates with borderline left ventricular function.[13] Characterizing the population for whom VA ECLS is beneficial begins with better understanding the variables that result in its selection.

Our study has important limitations. As with all chart reviews, the accuracy of our data is limited by omissions and ambiguities in clinical documentation, resulting in a risk for information bias. In excess of thirty percent of our cases lacked clear documentation of the indication for VA selection. Further, many of our variables were susceptible to misclassification bias. This decreases the validity of our primary objective – characterizing indications for VA ECLS in this population. Similarly, misclassification bias could decrease the accuracy of our secondary aim: to evaluate how the presence or absence of these variables influenced mortality. Our definitions for high inotropic support and ventricular dysfunction do not represent standardized nor validated definitions, but rather pragmatic classifications reflective of our practice. Clinical echocardiogram reports may be influenced by the quality of the images obtained, as well as variability between readers in interpretation and reporting parameters. Despite these limitations, the resulting differences in mortality on the basis of the presence or absence of these definitions suggest a measure of validity for what they attempt to capture: evidence of increasing disease severity. As a report of a single center experience, our results have limited

generalizability. Despite a high neonatal ECLS case volume and evaluation over a 14-year period, our sample size resulted in inadequate power to detect a statistically significant association between mortality and the presence of high inotropic support, ventricular dysfunction or both despite clinically meaningful increases in mortality associated with these variables (Figure 2 and Table IV).

Performing a randomized controlled trial assessing VA versus VV ECLS would be an ideal approach for obtaining an unbiased estimate of the effect of these modes on important patient outcomes. However, the likelihood of implementing such a trial is low. In its absence, collaborative, multi-center, prospective studies with objective and well-defined variables are needed to better approximate the risk and benefits of VA versus VV ECLS. Such studies should anticipate and account for the high risk of confounding bias through the collection of variables that may be associated with both the selection of cannulation mode and important outcomes such as death. Our findings suggest that the degree of inotropic refractory hypotension and echocardiographic ventricular dysfunction are critical variables for consideration.

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Table and Figure Legends

Figure 1.

ECLS = extracorporeal life support, VV = venovenous.

Figure 2.

Neither and both refer to absence or presence of both high inotropic support and ventricular dysfunction on echocardiogram, respectively. VA, venoarterial; ECLS, extracorporeal life support. Differences in mortality relative to "Neither" (reference) do not reach statistical significance in adjusted analyses; for "Both" $p = 0.05$ but is not < 0.05 (see Table 4).

Table I.

NOS = not otherwise specified, VV = venovenous.

Table II.

IQR, interquartile range; SD, standard deviation; MAS, meconium aspiration syndrome; PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome; NOS, not otherwise specified, PNA, pneumonia. $p > 0.05$ for all comparisons.

Table III.

IQR, interquartile range; SD, standard deviation; MAS, meconium aspiration syndrome; PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome; NOS, not otherwise specified, PNA, pneumonia. $p > 0.05$ for all comparisons.

Table IV.

OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; VA, venoarterial; ECLS, extracorporeal life support

Table I. Specified primary indications for selection of venoarterial extracorporeal life support

Primary Indication	*Frequency*	*Percent*
Total	**39**	
Specific Clinical Concerns:	**23**	**59.0**
Severity of Hypotension/Inotropic Support	6	15.4
Ventricular Dysfunction on Echocardiogram	4	10.3
Severity of Pulmonary Hypertension, Clinical/NOS	2	5.1
Severity of Ductal Shunt Gradient	1	2.6
Poor Cardiac Function, Clinical/NOS	1	2.6
Respiratory and Cardiac Failure, Clinical/NOS	1	2.6
Right Ventricular Dilatation on Echocardiogram	1	2.6
Concern for Premature Ductal Closure	1	2.6
Degree of Hypoxemia	1	2.6
Concern for Unclear Disease Etiology	1	2.6
Active CPR/Chest Compressions	4	10.3
Technical Size Limitations:	**4**	**10.2**
VV Not Attempted Due To Patient Size	1	2.6
VV Attempted, Unable To Insert	3	7.7
Unclear or Not Specified	**12**	**30.8**

Table II. Baseline characteristics by documented primary indication for venoarterial extracorporeal life support

	Total	**Clinical**	**Unspecified**	**Technical**
Subjects	39	23	12	4
Birth gestational age (weeks)				
Median (IQR)	39.0 (37.0-40.0)	39.0 (37.4-40.0)	38.5 (36.5-39.5)	39.5 (37.5-40.2)
Birth weight (kilograms)				
Median (IQR)	3.21 (2.80-3.67)	3.21 (2.80-4.18)	3.34 (2.75-3.59)	3.16 (2.51-3.50)
Sex				
Male	24 (62%)	14 (61%)	8 (67%)	2 (50%)
Female	15 (38%)	9 (39%)	4 (33%)	2 (50%)
Race				
White	18	12 (52%)	4 (33%)	2 (50%)
Black	15	7 (30%)	6 (50%)	2 (50%)
Other	6	4 (17%)	2 (17%)	0 (0%)
One minute Apgar score	n = 37	n = 22	n = 11	n = 4
Mean (SD)	4.5 (2.9)	4.5 (2.7)	4.1 (3.3)	5.0 (3.6)
Diagnosis				
MAS	7 (18%)	3 (13%)	3 (25%)	1 (25%)
PPHN	20 (51%)	13 (57%)	6 (50%)	1 (25%)
Other (RDS, Respiratory Failure NOS, PNA/Sepsis)	12 (31%)	7 (30%)	3 (25%)	2 (50%)
Oxygenation Index	n = 30	n = 16	n = 11	n = 3
Median (IQR)	43.3 (34.5-61.5)	42.3 (26.2-54.2)	53.2 (39.2-72.2)	36.7 (25.6-80.0)

Table III. Baseline characteristics by presence of common indications for venoarterial extracorporeal life support.

	Neither	High Inotropic Support Only	Ventricular Dysfunction Only	Both
Subjects (n = 39)	8 (21%)	15 (38%)	4 (10%)	12 (31%)
Birth gestational age (weeks)				
Median (IQR)	39.2 (37.5-40.0)	38.0 (36.5-40.0)	39.5 (38.0-40.5)	39.2 (37.8-40.0)
Birth weight (kilograms)				
Median (IQR)	3.35 (3.01-4.12)	2.99 (2.79-3.59)	3.33 (2.99-4.30)	3.56 (2.60-3.74)
Sex				
Male	5 (63%)	10 (67%)	2 (50%)	7 (58%)
Female	3 (38%)	5 (33%)	2 (50%)	5 (42%)
Race				
White	4 (50%)	7 (47%)	0 (0%)	7 (58%)
Black	4 (50%)	5 (33%)	4(100%)	2 (17%)
Other	0 (0%)	3 (20%)	0 (0%)	3 (25%)
One minute Apgar score	n = 8	n = 14	n = 4	n = 11
Mean (SD)	3.6 (2.8)	4.8 (2.8)	5.5 (3.7)	4.3 (3.1)
Diagnosis				
MAS	3 (38%)	2 (13%)	1 (25%)	1 (8%)
PPHN	3 (25%)	8 (53%)	2 (50%)	7 (58%)
Other (RDS, Respiratory Failure NOS, PNA/Sepsis)	2 (38%)	5 (33%)	1 (25%)	4 (33%)
Oxygenation Index	n = 7	n = 10	n = 4	n = 9
Median (IQR)	44.2 (35.1-80.0)	54.6 (45.0-72.2)	31.7 (25.7-45.5)	39.2 (28.8-42.6)

Table IV. Common indications for VA ECLS: association with in-hospital mortality in univariate and multivariate analysis.

Mortality Effect Estimate	*OR (95% CI)*	*aOR (95% CI)*	*p-value*
	Univariate	**Multivariate**	
Common VA ECLS Indications			
Neither High Inotropic Support or Ventricular Dysfunction	**Reference**	**Reference**	**-**
High Inotropic Support Only	1.75 (0.15-20.2)	6.89 (0.29-165)	0.23
Ventricular Dysfunction Only	2.33 (0.11-51.0)	2.05 (0.47-89.8)	0.71
Both High Inotropic Support and Ventricular Dysfunction	7.00 (0.64- 75.7)	30.0 (0.98-913)	0.05
Multivariate Model Covariates:			
One Minute Apgar Score	-	0.69 (0.45 – 1.03)	0.07
Gestational Age (per week)	-	1.56 (0.78-3.25)	0.20
Birth Weight (per kilogram)	**-**	3.13 (0.96 – 10.2)	0.06

Figure 1.

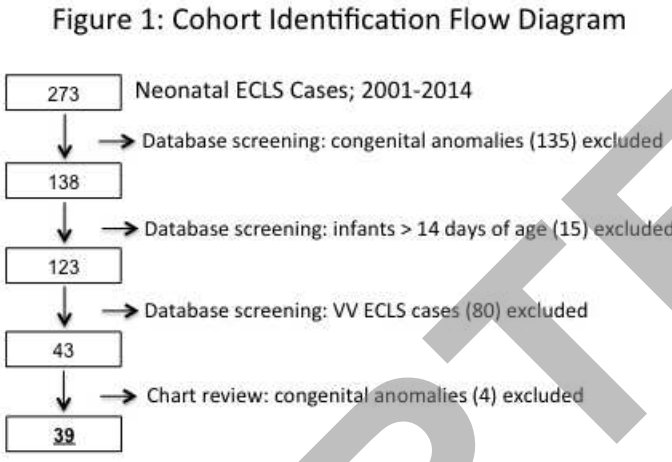

Figure 2.